Use of uridine triacetate for the management of fluorouracil overdose

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Purpose. The use of uridine triacetate for the management of fluorouracil toxicity is reported.

Summary. A 55-year-old man with malignant neoplasm of the sigmoid colon (stage IIIc) was seen in an outpatient chemotherapy center for his first six-month regimen of leucovorin calcium, fluorouracil, and oxaliplatin. Fluorouracil 2400 mg/m² i.v. was prescribed to be given over the next 46 hours at a home infusion center. Due to a medication error, a home infusion pharmacist incorrectly programmed the 46-hour infusion of fluorouracil to be administered over 4 hours. To manage the fluorouracil overdose, the physician decided to start the patient on uridine triacetate. The patient received his first dose of uridine triacetate 18 hours after the fluorouracil overdose. He was admitted to the hospital for observation and daily laboratory tests during treatment with uridine triacetate. He received ondansetron (as the hydrochloride salt) 8 mg orally 20 minutes before each dose of uridine triacetate to prevent nausea and vomiting. Uridine triacetate 11 g every 6 hours was administered orally for a total of 20 doses. It was mixed with applesauce at the time of administration and followed with 8 oz of water. The patient’s laboratory values remained stable. The patient did not experience any nausea or vomiting during treatment. He was discharged from the hospital on day 5, with no clinical complications and an Eastern Cooperative Oncology Group Performance score of 0.

Conclusion. A patient with colon cancer who had received an overdose of fluorouracil was successfully treated with a five-day course of oral uridine triacetate.

Index terms: Antidotes; Antiemetics; Antineoplastic agents; Colonic neoplasms; Dosage; Errors, medication; Fluorouracil; Injections; Leucovorin calcium; Nausea; Ondansetron hydrochloride; Oxaliplatin; Pharmacists; Poisoning; Toxicity; Uridine triacetate; Vomiting

Fluorouracil is a fluorinated pyrimidine antimetabolite used in various chemotherapeutic regimens.4,5 Fluorouracil by itself is inert, requiring cellular uptake and metabolic activation in order to exert cytotoxicity.6 After intravenous administration, fluorouracil is metabolized intracellularly through a complex pathway to the 5’-monophosphate nucleotide and several other cytotoxic metabolites. Eighty-five percent of fluorouracil is inactivated hepatically via dihydropyrimidine dehydrogenase; the other 15% is metabolized to fluorodeoxyuridine monophosphate (F-dUMP), fluorodeoxyuridine triphosphate (F-dUTP), and floxuridine triphosphate (FUTP).1-3

It is thought that the main mechanism through which fluorouracil works is the inhibition of thymidylate synthase by F-dUMP.1,2 In the presence of folates, F-dUMP binds tightly to thymidylate synthase to prevent the production of thymidine, which is an essential building block of DNA.1,2 F-dUMP will also be metabolized to F-dUTP, which can take the place of thymidine in the building of the DNA strand; this will lead to DNA strand fragmentation.1 In addition, the metabolite FUTP will take the place of uridine triphosphate during RNA synthesis, which will cause disruption of RNA functions.1,3

Based on a root-cause analysis of a fluorouracil incident published by the Institute for Safe Medication

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Drs. McEvilly and Popelas have declared no potential conflicts of interest. Dr. Tremmel is employed by Wellstat Therapeutics Corporation, the manufacturer of the uridine triacetate used in the case described herein.
Practices Canada, a patient could be at excess risk for fluorouracil toxicity if the administered dose is at least 10% greater than the intended dose or if the infusion rate is at least 25% greater than the intended rate for the patient. In cases where the overdose was caused by either a dose or infusion rate that was twice the intended value, the outcome was consistently fatal.

Uridine is a naturally occurring nucleoside and is metabolized to uridine triphosphate in the body. Uridine triphosphate competitively inhibits FUTP incorporation into RNA, thereby decreasing its lethal effects.

Uridine triacetate (formerly known as visturonidine) was granted orphan drug status by the Food and Drug Administration (FDA) as an antidote for fluorouracil toxicity on May 1, 2009. It is a biochemical modulator agent that was first investigated for its use to decrease the adverse effects of fluorouracil in patients requiring higher doses of the drug due to progressive disease. As with any antidote, it is critical to begin treatment as soon as possible after exposure or overdose. Uridine triacetate should be given between three hours and four days after a fluorouracil overdose. Theoretically, if uridine triacetate is given at least three hours after the administration of a fluorouracil overdose, it should not cause a significant decrease in the antineoplastic activity of fluorouracil. However, the patient’s chemotherapy schedule could be adversely affected. In addition, uracil (a byproduct of uridine triacetate breakdown) can decrease the urinary clearance of fluorouracil if given sooner than three hours after an overdose.

Administration of uridine triacetate after a fluorouracil overdose reduces toxic effects on the gastrointestinal tract and the hematopoietic system. However, the administration of therapeutically effective doses of uridine is not feasible in clinical practice.

Attempts to treat patients with uridine orally have been unsuccessful because the oral dosage form is only about 7% bioavailable. The dose needed orally for clinical effectiveness is 10 g. At this dose, orally administered uridine would lead to severe nausea and osmotic diarrhea. The intravenous formulation has also been unsuccessful due to a high incidence of extravasation and phlebitis.

Uridine triacetate delivers approximately eightfold more bioavailable uridine when administered to animals or humans than oral administration of equimolar doses of uridine itself. Because it is lipophilic, uridine triacetate crosses the gastrointestinal mucosa much more readily than does uridine. Once absorbed, uridine triacetate is metabolized to uridine and acetate. The increased bioavailability of uridine triacetate leads to higher serum concentrations of uridine. As noted previously, uridine has the ability to competitively inhibit the incorporation of FUTP into RNA, thereby decreasing the severity of toxicities.

We report the case of a patient with colon cancer who was successfully treated with uridine triacetate after receiving an overdose of fluorouracil.

Case report

A 55-year-old, 77.9-kg man with malignant neoplasm of the sigmoid colon (stage IIIC) status postresection two months prior arrived at our outpatient chemotherapy center for his first chemotherapy treatment. His chemotherapeutic regimen included leucovorin calcium, fluorouracil, and oxaliplatin (a regimen known as FOLFOX), which was to be given every two weeks for 12 cycles. The patient had no other significant medical history.

On day 1 of cycle 1, the patient received i.v. leucovorin calcium 776 mg, i.v. fluorouracil 776 mg, and i.v. oxaliplatin 165 mg. The patient also received aprepitant 125 mg orally, i.v. dexamethasone 10 mg (as the sodium phosphate salt), and i.v. palonosetron 0.25 mg (as the hydrochloride salt) before administration of his chemotherapy. Fluorouracil was then prescribed at a dosage of 2400 mg/m² i.v. to be given over the next 46 hours through a home infusion center.

That evening, the patient called his physician to explain that the entire contents of the fluorouracil continuous infusion had been administered and that the bag was empty. The 46-hour infusion had been administered over 4 hours. It was discovered that the infusion pump had been programmed incorrectly by the home infusion pharmacist.

Obtaining uridine triacetate.

To manage the fluorouracil overdose, the patient’s physician decided to start the patient on uridine triacetate and contacted the manufacturer (Wellstat Therapeutics Corporation, Gaithersburg, MD) via the Wellstat Safety hot line (443-831-5626) to obtain information on accessing the drug.

Uridine triacetate is an investigational drug supplied for emergency use only, and prior approval from FDA is mandatory for its use in the United States. A physician must contact FDA and request in writing an emergency use of an Investigational New Drug (IND) for a specific patient. Before uridine triacetate is assigned, FDA must receive the following information:

- The patient’s medical history, including diagnosis, status, prior therapy, response to prior therapy, and rationale for the use of uridine triacetate,
- The proposed treatment regimen as received from Wellstat Therapeutics,
- A copy of the letter of authorization from Wellstat Therapeutics stating that it is willing to provide the medication for single-patient use,
- A statement from the physician indicating that informed consent will be received from the patient before...
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administration of the first dose of uridine triacetate, and
- The physician’s curriculum vitae, a copy of his or her licensure, and his or her telephone number, fax number, and e-mail address.\(^\text{18}\)

In addition, investigational review board approval must be obtained within five working days of initiating treatment. Once emergency use is authorized by FDA, a Single Patient IND (SPI) will be given to the provider from FDA, which must be given to Wellstat Therapeutics as soon as possible so the company can begin the process of preparing and shipping the medication. The SPI will be followed by a letter of approval from FDA. Wellstat Therapeutics will provide an informed consent for the patient to sign and a copy of the treatment regimen for fluorouracil overdose.

Treatment course and outcome. The patient received his first dose of uridine triacetate 18 hours after the fluorouracil overdose. He was admitted to the hospital for observation and daily laboratory tests. He received ondansetron (as the hydrochloride salt) 8 mg orally 20 minutes before each dose of uridine triacetate to prevent nausea and vomiting. Uridine triacetate 11 g every 6 hours was administered orally for a total of 20 doses. It was mixed with applesauce at the time of administration and followed with 8 oz of water. The patient also received 1 subcutaneous dose of pegfilgrastim 6 mg on day 2 of hospitalization.

The patient’s laboratory test values remained stable, with a transient increase in white blood cell counts, which was attributable to the administration of pegfilgrastim. The patient continued his FOLFOX regimen five weeks after the original administration date, only one week late. The delay in treatment was due to a mild increase in his aspartate transaminase and alanine transaminase values (118 and 282 units/L, respectively). His alkaline phosphatase level was normal. The patient did not experience any nausea or vomiting during uridine triacetate treatment. He was discharged from the hospital on day 5, after taking his last dose of uridine triacetate, with no clinical complications and an Eastern Cooperative Oncology Group Performance score of 0.\(^\text{19}\)

Discussion

The National Institutes of Health has estimated that 275,000 people receive fluorouracil in the United States each year.\(^\text{20}\) Approximately 3% of those patients develop a serious adverse reaction to the drug, and more than 1,300 patients die annually from fluorouracil overdose. Until now, there has been no antidote for fluorouracil toxicity, only supportive care (e.g., granulocyte colony-stimulating factors, hydration, antiemetics, antibiotics).

According to information obtained from Wellstat Therapeutics, the procedure for obtaining uridine triacetate in the United States for emergency use will soon be updated and transitioned to an expanded-access protocol. The protocol is currently under FDA review.\(^\text{21}\) When enacted, this protocol will allow for greater access to uridine triacetate when needed as an antidote to treat patients at increased risk of fluorouracil toxicity due to overdose or impaired fluorouracil elimination. The recommended dosage of uridine triacetate, however, will remain unchanged.

Von Borstel et al.\(^\text{6}\) described 17 patients who experienced an accidental fluorouracil overdose that required emergency treatment with uridine triacetate. While all 17 patients recovered from the overdose without complications, 13 of the overdoses were considered lethal based on the dose and administration rate of fluorouracil. The authors presented historical data from 13 other cases of fluorouracil overdose in which the patients did not receive uridine triacetate. Eleven of those 13 patients died.

Bamat et al.\(^\text{22}\) described 35 cases of accidental fluorouracil overdose in which the patients were treated with uridine triacetate. While all 35 patients recovered from the overdose without complications, 27 of the overdoses were considered lethal based on the dose and administration rate of fluorouracil. The authors also presented historical data from 33 other cases in which the patients did not receive uridine triacetate; 29 of those patients died.

Uridine triacetate is an orange-flavored powder supplied in a 250-g container. The dosage is 11 g every six hours administered orally for a total of 20 doses (11 g of the powder contains 10 g of uridine triacetate). Uridine triacetate absorption is not affected by food, and it is recommended that it be mixed with pudding, yogurt, or applesauce and followed with a glass of water.\(^\text{8}\)

Rarely, administration of uridine triacetate is associated with nausea and vomiting due to the slightly bitter taste of the drug. However, many patients receiving this drug are also being treated with chemotherapy regimens that consist of emetogenic agents and are likely to have received antiemetics before the overdose. If the patient vomits within two hours of taking a dose of uridine triacetate, the entire dose should be repeated within 15 minutes of vomiting. The next dose should still be taken at the regularly scheduled time, regardless of whether the patient vomits again. If nausea or vomiting is an issue, a short-acting serotonin type 3-receptor antagonist, such as ondansetron, may be given 20–30 minutes before each dose. Other adverse effects may include allergic reactions ranging from a mild rash to anaphylaxis.\(^\text{8}\)

Potential drug interactions of importance include medications
that may interfere with the absorption of uridine triacetate. These agents include but are not limited to kapecolin, bismuth, sucralfate, and cholestyramine. These medications must be discontinued altogether during treatment.8

The absorption of uridine triacetate is critical to ensure proper serum levels of the drug. Serum uridine triacetate levels may be measured to examine uracil:dihydrouracil ratios, which indicate the catabolism of uracil and uracil-containing compounds. Levels should be measured before administration of the first dose, two hours after the first dose, and two hours after the last dose. The dosage of uridine triacetate is fixed and two hours after the last dose. The goal serum uridine triacetate concentration is above 70 μM/mL to offset fluorouracil toxicities.23

Dosages of uridine triacetate are not adjusted, regardless of patient age or sex, dose of fluorouracil, or hepatic or renal function.

Conclusion
A patient with colon cancer who had received an overdose of fluorouracil was successfully treated with a five-day course of oral uridine triacetate.

References